

What is claimed is:

1. A method for *in vivo* delivery of a desired composition into human or animal central nervous system (CNS) or spinal cord, wherein the method comprises administering to the human or animal a composition comprising a non-toxic, proteolytic fragment of tetanus toxin (TT) in association with at least a molecule having a biological function and said composition is capable of *in vivo* retrograde axonal transport and transynaptic transport into the CNS or the spinal cord of the human or animal and of being delivered at different areas of the CNS or the spinal cord.
2. The method according to claim 1, wherein the composition is administered into a muscle.
3. The method according to claim 1, wherein the composition is administered into a muscle in the vicinity of a neuromuscular junction.
4. The method according to claim 1, wherein the muscle is selected in relation with the desired area of the CNS or spinal cord.
5. The method according to claim 1, wherein the composition is administered into neuronal cells.
6. The method according to claim 1, wherein the composition comprises a non-toxic, proteolytic fragment of tetanus toxin (TT) comprising a fragment C and a fragment B or a fraction thereof of at least 11 amino acid residues in association with at least a molecule having a biological function selected from the group consisting of a protein for compensation or modulation of functions under the control of the CNS or the spinal cord

or modulation of functions in the CNS or the spinal cord or a protein to be delivered by gene therapy expression system to the CNS or the spinal cord.

7. The method according to claim 1, wherein the composition comprises a non-toxic, proteolytic fragment of tetanus toxin (TT) comprising a fragment C and a fragment B or a fraction thereof of at least 11 amino acid residues and a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245 in association with at least a molecule having a biological function selected from the group consisting of protein for the compensation or the modulation of functions under the control of the CNS or the spinal cord or protein to be delivered by gene therapy expression system to the CNS or the spinal cord.

8. The method according to claim 6 or claim 7, wherein the molecule is selected from the group consisting of protein SM, BDNF (Brain-derived neurotrophic factor), NT-3 (Neurotrophin-3), NT-4/5, GDNF (Glial cell-line-derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SPI3 (Serine Protease Inhibitor protein), ICE (Interleukin-1 $\beta$  converting enzyme), Bcl-2, GFP (green fluorescent protein), endonucleases like I-SceI or CRE, antibodies, or drugs specifically directed against neurodegenerative diseases such as latero spinal amyotrophy (LSA).

9. The method according to claim 8, wherein the composition comprises a combination of at least two of said molecules.

10. The method according to claim 8, wherein the molecule is located upstream from the fragment of tetanus toxin.

11. The method according to claim 8, wherein the molecule is located downstream from the fragment of tetanus toxin.

12. The method according to claim 1, which comprises administering to the human or animal a vector containing nucleotides encoding the composition, wherein the vector is capable of *in vivo* expression in a muscle and this product is capable of migrating to the CNS or spinal cord.

13. The method according to claim 12, wherein said vector comprises a promoter and an enhancer capable of expressing the nucleotides contained in said vector in the muscle.

14. The method according to claim 13, wherein said vector is the plasmid pCMV-LacZ-TTC which has been deposited at the C.N.C.M. on August 12, 1997, under the registration number I-1912.

15. The method according to claim 12 or 13, wherein said vector is administered into the muscle.

16. The method according to claim 12 or 13, wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being transported and expressed directly in neurons.

17. A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction thereof of at least 11 amino acid residues capable of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

18. A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction thereof of at least 11 amino acid residues and a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245 capable of transferring *in vivo* a protein, a peptide or a polynucleotide through a neuromuscular junction and at least one synapse.

19. An amino acid variant fragment having the same properties as the hybrid fragment of tetanus toxin according to claims 17 or 18.

20. A polynucleotide variant fragment capable of hybridization under stringent conditions with the natural tetanus toxin sequence.

21. A composition containing an active molecule in association with a hybrid fragment of tetanus toxin according to claims 17 or 18 or with an amino acid variant fragment according to claim 16.

22. The composition according to claim 21, wherein the active molecule is selected from the group consisting of protein SMN, BDNF (Brain-derived neurotrophic factor), NT-3, NT-4/5, GDNF (Glial cell-line derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SP13 (Serine Protease Inhibitor protein), ICE, Bcl-2, GFP (green fluorescent protein), endonucleases like I-SceI or CRE, antibodies or drugs specifically directed against neurodegenerative diseases such as latero spinal amyotrophy (LSA).

23. The composition according to claim 21, wherein the active molecule is a polynucleotide encoding a protein or a polypeptide with a promoter capable of expression in neurons, and optionally an enhancer.

24. A vector comprising a promoter capable of expression in muscle cells and optionally an enhancer, a nucleic acid sequence coding for the fragment of tetanus toxin according to claims 17 or 18 or with an amino acid variant fragment according to claim 19 associated with a polynucleotide coding for a protein or a polypeptide.

25. A method of treatment of a patient or an animal affected with CNS or spinal cord disease, which comprises delivering a composition according to claims 21, 22, or 23 to the patient or animal in an amount effective for treatment of the CNS or spinal cord disease.

26. A method of treatment of a patient or an animal affected with CNS or spinal cord disease, which comprises delivering a vector according to claim 24 to the patient or animal in an amount effective for treatment of the CNS or spinal cord disease.

27. The method according to claim 1, which comprises administering to the human or animal a cell or a vector containing nucleotides encoding the composition, wherein the cell or vector is capable of *in vivo* expression in neuronal cells or precursor of neuronal cells and wherein said cell is reimplanted into the CNS or spinal cord.

28. The method according to claim 27 wherein said cell or vector comprises a promoter and an enhancer capable of expressing the nucleotides contained in said cell in neuronal cells or precursors of neuronal cells.

29. The method according to claim 27 or 28 wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being expressed directly in neurons.

30. The method according to claim 27 or 28 wherein the molecule is a nucleotide encoding for a protein or a polypeptide linked chemically to the fragment of tetanus toxin and being expressed directly in neurons.

31. A cell or vector comprising a promoter capable of expression in neuronal cells or precursors of neuronal cells and optionally an enhancer, a nucleic acid sequence coding for the fragment of tetanus toxin according to claims 17 or 18 or with an amino acid variant fragment according to claim 19 associated with a polynucleotide coding for a protein or a polypeptide.

32. A method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin, wherein the method comprises administering to the neuron a TrkB receptor agonist or a TrkB receptor antagonist in an amount sufficient to modulate the neuronal transport of the tetanus toxin or the fusion protein.

33. The method according to claim 32, wherein the TrkB receptor agonist is administered, thereby increasing the internalization of the tetanus toxin or fusion protein at a neuromuscular junction.

34. The method according to claim 33, wherein the TrkB receptor agonist is a neurotrophic factor that activates a TrkB receptor.

35. The method according to claim 34, wherein the neurotrophic factor is a Brain Derived Neurotrophic Factor or a Neurotrophin 4.
36. The method according to claim 33, wherein the TrkB receptor agonist is an antibody that binds to a TrkB receptor, thereby activating the TrkB receptor.
37. The method according to any one of claims 35 or 36, wherein the internalization of the fusion protein at the neuromuscular junction is increased.
38. The method according to claim 32, wherein the TrkB receptor antagonist is administered, thereby decreasing the internalization of the tetanus toxin or fusion protein at a neuromuscular junction.
39. The method according to claim 38, wherein the TrkB receptor antagonist is an antibody that binds to a TrkB receptor agonist, thereby reducing activation of a TrkB receptor.
40. The method according to claim 39, wherein the TrkB receptor agonist is a neurotrophic factor that activates a TrkB receptor.
41. The method according to claim 40, wherein the neurotrophic factor is a Brain Derived Neurotrophic Factor or a Neurotrophin 4.
42. The method according to claim 42, wherein the internalization of the tetanus toxin at the neuromuscular junction is decreased.
43. The method according to claim 40, wherein the neurotrophic factor is administered concurrently with the fusion protein.

44. A method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin, wherein the method comprises administering to the neuron a GFR $\alpha$ /cRET receptor agonist or a GFR $\alpha$ /cRET receptor antagonist in an amount sufficient to modulate the neuronal transport of the tetanus toxin or the fusion protein.

45. The method according to claim 44, wherein the GFR $\alpha$ /cRET receptor agonist is administered, thereby increasing the internalization of the tetanus toxin or fusion protein at a neuromuscular junction.

46. The method according to claim 45, wherein the GFR $\alpha$ /cRET receptor agonist is a neurotrophic factor that activates a GFR $\alpha$ /cRET receptor.

47. The method according to claim 46, wherein the neurotrophic factor is a Glial-Derived Neurotrophic Factor.

48. The method according to claim 44, wherein the GFR $\alpha$ /cRET receptor agonist is an antibody that binds to a GFR $\alpha$ /cRET receptor, thereby activating the GFR $\alpha$ /cRET receptor.

49. The method according to any one of claims 46 or 47, wherein the internalization of the fusion protein at the neuromuscular junction is increased.

50. The method according to claim 44, wherein the GFR $\alpha$ /cRET receptor antagonist is administered, thereby decreasing the internalization of the tetanus toxin or fusion protein at a neuromuscular junction.



51. The method according to claim 50, wherein the GFR $\alpha$ /cRET receptor antagonist is an antibody that binds to a GFR $\alpha$ /cRET receptor agonist, thereby reducing activation of a GFR $\alpha$ /cRET receptor.

52. The method according to claim 51, wherein the GFR $\alpha$ /cRET receptor agonist is a neurotrophic factor that activates a GFR $\alpha$ /cRET receptor.

53. The method according to claim 52, wherein the neurotrophic factor is a Glial-Derived Neurotrophic Factor.

54. The method of claim 53, wherein the internalization of the tetanus toxin at the neuromuscular junction is decreased.

55. The method according to claim 47, wherein the neurotrophic factor is administered concurrently with the fusion protein.

56. A composition, comprising a TrkB receptor agonist and a fusion protein comprising a fragment C of the tetanus toxin fused to a second protein.

57. The composition according to claim 56, wherein, the TrkB receptor antagonist is a neurotrophic factor that activates a TrkB receptor.

58. The composition according to claim 57, wherein the neurotrophic factor is a Brain Derived Neurotrophic Factor or a Neurotrophin 4.

59. A composition, comprising a GFR $\alpha$ /cRET receptor agonist and a fusion protein comprising a fragment C of the tetanus toxin fused to a second protein.

60. The composition according to claim 59, wherein, the GFR $\alpha$ /cRET receptor antagonist is a neurotrophic factor that activates a GFR $\alpha$ /cRET receptor.

61. The composition according to claim 60, wherein the neurotrophic factor is Glial-Derived Neurotrophic Factor.

62. A method of detecting an effect of a compound on neuronal transport, comprising administering to a neuron the compound and a fusion protein comprising a fragment C of the tetanus toxin fused to a second protein, wherein the second protein is encoded by a reporter gene, and detecting the second protein to determine the effect of the compound on neuronal transport.

63. The method according to claim 62, wherein the compound is a neurotrophic factor.

64. A method of screening for a compound that reduces or prevents transport of a tetanus toxin in a neuron, comprising administering to the neuron the compound and a fusion protein comprising a fragment C of the tetanus toxin fused to a second protein, wherein the second protein is encoded by a reporter gene, detecting the second protein, and selecting the compound that reduces or prevents the neuronal transport of the fusion protein.

65. The method according to claim 64, wherein the second protein is detected at a neuromuscular junction.